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SCIENTIFIC DATA REVIEWS
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

FEB - 7 1995

MEMORANDUM

SUBJECT: Difenoconazole (Dividend®): Dietary Exposure Analysis for the Proposed Use on Imported Wheat, Barley and Rye Grain (PP# 2F4051)

FROM: Jennifer M. Wintersteen *Jennifer Wintersteen*
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TO: C. Giles-Parker/J. Stone, PM Team 22
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THROUGH: Elizabeth A. Doyle, Section Head *E.A. Doyle*
Science Analysis Branch
Health Effects Division *Woban*

Action Requested

Provide estimates of chronic and acute dietary risk for the proposed use of difenoconazole on imported wheat, barley and rye grain at 0.1 ppm, 0.05 ppm on animal products and 0.01 ppm on milk. **This is the first permanent food use petition for this chemical.** Only temporary or time-limited tolerances currently exist for difenoconazole.

Discussion

1. Toxicological Endpoints: For chronic dietary exposure the Reference Dose (RfD) of 0.01 mg/kg bwt/day is based on a NOEL of 0.96 mg/kg/day and an uncertainty factor of 100. The NOEL is taken from a long term rat feeding study and the effect is hepatotoxicity at 24.12 mg/kg/day in males. The RfD has been approved by the HED RfD Peer Review Committee [G. Ghali memo, 2/24/94].

Based on weight of the evidence, difenoconazole has been classified as a Category C (possible human) carcinogen. The Carcinogenicity Peer Review recommended that for the purposes of risk characterization, the Reference Dose approach should be used for quantification of human risk (E. Rinde Peer Review document, 7/27/94)

A Toxicology Endpoint Selection Document for difenoconazole (J. Rowland and M. Van Gemert memo, 6/17/94) indicates that developmental toxicity is of concern. In order to calculate the acute dietary risk a NOEL of 25 mg/kg bwt/day was supplied in the same memo as appropriate for acute dietary assessment.



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2. Residue Information: Currently there are no published tolerances for difenoconazole in 40 CFR. CBTS recommends for the proposed uses on imported wheat, rye and barley grain (0.1 ppm), straw (0.1 ppm) and forage (0.1 ppm) as well as animal tolerances from resulting secondary residues as follows (G. Kramer memo, 11/21/94 and 1/4/95 personal communication):

Eggs	0.05 ppm
Milk	0.01 ppm
Meat ¹	0.05 ppm
Fat ¹	0.05 ppm
Meat By-Products ¹	0.05 ppm

The DRES analysis is based on the parent compound only and not metabolites (G. Kramer memo to HED Metabolism Committee, 7/22/94).

No refinements of percent crop treated or anticipated residue data were made to the DRES analysis. Tolerance level residues and 100% crop treated assumptions were made for both chronic and acute analyses.

3. Chronic Exposure Analysis: For chronic dietary exposure the Theoretical Maximum Residue Contribution (TMRC) for the general U.S. population and the highest exposed subgroups is as follows (as percent of the Reference Dose):

U.S. population	4%
Children (1-6)	.9%
Non-nursing Infants (< 1)	10%

The TMRC from the proposed import use on wheat, barley and rye is 4.2×10^{-4} mg/kg/day, representing 4% of the RfD for the overall U.S. population. A summary of the chronic exposure estimates is attached as Table 2.

4. Acute Exposure: The DRES detailed acute exposure analysis evaluates individual food consumption as reported by respondents in the USDA 77-78 Nationwide Food Consumption Survey (NFCS) and estimates the distribution of single day exposures through the diet for the U.S. population and certain subgroups. The analysis assumes uniform distribution of difenoconazole in the commodity supply. Since the toxicological effect to which high end exposure is being compared to in this analysis is developmental toxicity the subgroup of concern is females (13+ years). For substances whose acute NOEL is based on animal studies, the Agency is not generally concerned unless the MOE is below 100.

Using the proposed wheat, barley and rye tolerances of 0.1 ppm and meat, milk and egg tolerances, the MOE for the subgroup females 13+ for high end exposure is 62,500. The estimated percent of potential person days that are consumer days of any commodity for which difenoconazole has proposed tolerances is 92% of the population. The table below provides the calculated MOE for the females 13+ subgroup.

¹ Meat of cattle, goats, horses, hogs, poultry and sheep

DRES Subgroup	High End Exposure (mg/kg bwt/day)	MOE NOEL/High Exposure
Females (13+ years)	0.0004	62,500

This is the first time that acute exposure has been calculated for difenoconazole. The calculated MOE is well above the level that the Agency generally considers negligible for the females 13+ subgroup used in the DRES acute program and thus acute exposure is not expected to be a problem. A table of distribution of exposures in this analysis is attached as Table 3.

Conclusions

The chronic and acute dietary risk estimates are not of concern for the proposed import tolerances for difenoconazole on wheat, barley and rye.

Attachments

cc: DRES, CBTS (G. Kramer), Tox II (J. Rowland), Caswell #955

Table 1.

CHEMICAL INFORMATION FOR CASWELL NUMBER 955

DATE: 02/01/95

PAGE: 1

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Difencconazole (Dividend) Caswell #955 CAS No. 119446-68-3 A.I. CODE: 128947 CFR No.	Zyr feeding- rat NOEL= 0.9600 mg/kg 20.00 ppm LEL= 24.1200 mg/kg 500.00 ppm ONCO: Pending	Reductions in cumulative body weight gains. Referred to Carcinogenic- ity Peer Review Committee	ADI UF -->100 Opp RfD= 0.0100000 EPA RfD= 0.0000000	No data gaps.	RfD/PR reviewed 01/06/94

FOOD CODE	FOOD NAME	PETITION NUMBER	TOLERANCE (PPM)	
			NEW	PENDING PUBLISHED
24001AA	BARLEY	2E4071	0.100000	
24005AA	RYE-ROUGH	2E4071	0.100000	
24005GA	RYE-GERM	2E4071	0.100000	
24005MA	RYE-FLOUR	2E4071	0.100000	
24007AA	WHEAT-ROUGH	2E4107	0.100000	
24007GA	WHEAT-GERM	2E4107	0.100000	
24007HA	WHEAT-BRAN	2E4107	0.100000	
24007MA	WHEAT-FLOUR	2E4107	0.100000	
50000DB	MILK-NON-FAT SOLIDS	2E4107	0.010000	
50000FA	MILK-FAT SOLIDS	2E4107	0.010000	
50000SA	MILK SUGAR (LACTOSE)	2E4107	0.010000	
53001BA	BEEF-MEAT BYPRODUCTS	2E4107	0.050000	
53001BB	BEEF(ORGAN MEATS)-OTHER	2E4107	0.050000	
53001DA	BEEF-DRIED	2E4107	0.050000	
53001FA	BEEF(BONELESS)-FAT	2E4107	0.050000	
53001KA	BEEF(ORGAN MEATS)-KIDNEY	2E4107	0.050000	
53001LA	BEEF(ORGAN MEATS)-LIVER	2E4107	0.050000	
53001MA	BEEF(BONELESS)-LEAN	2E4107	0.050000	
53002BA	GOAT-MEAT BYPRODUCTS	2E4107	0.050000	
53002BB	GOAT(ORGAN MEATS)-OTHER	2E4107	0.050000	
53002FA	GOAT(BONELESS)-FAT	2E4107	0.050000	
53002KA	GOAT(ORGAN MEATS)-KIDNEY	2E4107	0.050000	
53002LA	GOAT(ORGAN MEATS)-LIVER	2E4107	0.050000	
53002MA	GOAT(BONELESS)-LEAN	2E4107	0.050000	
53003AA	HORSE	2E4107	0.050000	
53005BA	SHEEP-MEAT BYPRODUCTS	2E4107	0.050000	
53005BB	SHEEP(ORGAN MEATS)-OTHER	2E4107	0.050000	
53005FA	SHEEP(BONELESS)-FAT	2E4107	0.050000	
53005KA	SHEEP(ORGAN MEATS)-KIDNEY	2E4107	0.050000	
53005LA	SHEEP(ORGAN MEATS)-LIVER	2E4107	0.050000	
53005MA	SHEEP(BONELESS)-LEAN	2E4107	0.050000	
53006BA	PORK-MEAT BYPRODUCTS	2E4107	0.050000	
53006BB	PORK(ORGAN MEATS)-OTHER	2E4107	0.050000	
53006FA	PORK(BONELESS)-FAT	2E4107	0.050000	
53006KA	PORK(ORGAN MEATS)-KIDNEY	2E4107	0.050000	
53006LA	PORK(ORGAN MEATS)-LIVER	2E4107	0.050000	
53006MA	PORK-LEAN	2E4107	0.050000	
55008BA	TURKEY-BYPRODUCTS	2E4107	0.050000	
55008LA	TURKEY-GIBLETS (LIVER)	2E4107	0.050000	
55008MA	TURKEY-FLESH(W/O SKIN)	2E4107	0.050000	

Table 1.

CHEMICAL INFORMATION FOR CASWELL NUMBER 955 DATE: 02/01/95 PAGE: 2

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Difenoconazole (Dividend) Caswell #955 CAS No. 119446-68-3 A.I. CODE: 128847 CFR No.	2yr feeding- rat NOEL= 0.9600 mg/kg 20.00 ppm LEL= 24.1200 mg/kg 500.00 ppm ONCO: Pending	Reductions in cumulative body weight gains. Referred to Carcinogenicity Peer Review Committee	ADI UF -->100 OPP RFD= 0.010000 EPA RFD= 0.000000	No data gaps.	RfD/PR reviewed 01/06/94

FOOD CODE	FOOD NAME	PETITION NUMBER	NEW	TOLERANCE (PPM)	PUBLISHED
55008MB	TURKEY-FLESH(+SKIN)	2F4107	0.050000		
55008MC	TURKEY-UNSPECIFIED	2F4107	0.050000		
55013BA	POULTRY, OTHER-BYPRODUCTS	2F4107	0.050000		
55013LA	POULTRY, OTHER-(LIVER)	2F4107	0.050000		
55013MA	POULTRY, OTHER-FLESH (+SKIN)	2F4107	0.050000		
55014AA	EGGS-WHOLE	2F4107	0.050000		
55014AB	EGGS-WHITE ONLY	2F4107	0.050000		
55014AC	EGGS-YOLK ONLY	2F4107	0.050000		
55015BA	CHICKEN-BYPRODUCTS	2F4107	0.050000		
55015LA	CHICKEN-GIBLETS(LIVER)	2F4107	0.050000		
55015MA	CHICKEN-FLESH(W/O SKIN)	2F4107	0.050000		
55015MB	CHICKEN-FLESH(+SKIN)	2F4107	0.050000		

Table 2: Summary of TMRCs and % of RfD for Difenoconazole on Wheat, Barley and Rye

CHEMICAL INFORMATION	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Difenoconazole (Difend)	Yr feeding - rat	Reductions in cumulative body weight gains.	ADI UF -->100 OPP RfD= 0.010000 EPA RfD= 0.000000	No data gaps.	RfD/PR reviewed 01/06/94
Caswell #955	NOEL= 0.9600 mg/kg				
CAS No. 119446-68-3	LEL= 20.00 ppm				
A.I. CODE: 128847	500.00 mg/kg				
CR No.	ONCO: Pending	Referred to Carcinogenicity Peer Review Committee			
POPULATION SUBGROUP					
U.S. POPULATION - 48 STATES		0.000000	0.000419	4.185220	4.185220
U.S. POPULATION - SPRING SEASON		0.000000	0.000407	4.072520	4.072520
U.S. POPULATION - SUMMER SEASON		0.000000	0.000414	4.143850	4.143850
U.S. POPULATION - FALL SEASON		0.000000	0.000430	4.297150	4.297150
U.S. POPULATION - WINTER SEASON		0.000000	0.000423	4.227580	4.227580
NORTHEAST REGION					
NORTH CENTRAL REGION		0.000000	0.000431	4.311880	4.311880
SOUTHERN REGION		0.000000	0.000426	4.264760	4.264760
WESTERN REGION		0.000000	0.000397	3.969360	3.969360
HISPANICS					
NON-HISPANIC WHITES		0.000000	0.000427	4.272370	4.272370
NON-HISPANIC BLACKS		0.000000	0.000484	4.842600	4.842600
NON-HISPANIC OTHERS		0.000000	0.000416	4.155290	4.155290
NURSING INFANTS (< 1 YEAR OLD)					
NON-NURSING INFANTS (< 1 YEAR OLD)		0.000000	0.000284	2.842130	2.842130
FEMALES (13+ YEARS, PREGNANT)		0.000000	0.000960	9.600910	9.600910
FEMALES 13+ YEARS, NURSING		0.000000	0.000296	2.955640	2.955640
CHILDREN (1-6 YEARS OLD)		0.000000	0.000357	3.569310	3.569310
CHILDREN (7-12 YEARS OLD)		0.000000	0.000947	9.469420	9.469420
MALES (13-19 YEARS OLD)		0.000000	0.000644	6.439890	6.439890
FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING)		0.000000	0.000462	4.618680	4.618680
MALES (20 YEARS AND OLDER)		0.000000	0.000357	3.567520	3.567520
FEMALES (20 YEARS AND OLDER, NOT PREG. OR NURS)		0.000000	0.000335	3.347750	3.347750
		0.000000	0.000270	2.704750	2.704750
TOTAL TMRC (MG/KG BODY WEIGHT/DAY)					
CURRENT TMRC*					
NEW TMRC**					
NEW TMRC AS PERCENT OF RfD					
DIFFERENCE AS PERCENT OF RfD					
EFFECT OF ANTICIPATED RESIDUES					
ARC					
%RfD					

*Current TMRC does not include new or pending tolerances.
 **New TMRC includes new, pending, and published tolerances.

Table 3: Acute Dietary Risk Analysis

NOEL = 25 mg/kg bwt/day
 DETAILED ACUTE ANALYSIS INCLUDING AR'S: ALL STATISTICS BASED ON USERS' DAILY CONSUMPTION 15:07 Wednesday, February 1, 1995 17

 *NAME: DIFENOCANAZOLE
 *CAS NO: 955
 *CAS NO: CFR NO: CFR
 *STATUS CODES: A B C
 *SHAUGHNESSY NO: 128847 B
 *LD: The LD value used in this analysis is 0.00025 / MG/KG of BODY WEIGHT/DAY
 *TOLERANCE DATA: No Tolerance Data Are Used--Without User Modifications.
 *FIVE INFO: No User Modifications.

 AR DATA: No User Modifications*

FEMALES(13+ YRS)

ESTIMATED % OF POTENTIAL	PERSON DAYS THAT ARE USER-DAYS	MG/KG BODY WEIGHT/DAY	AS PERCENT OF RDV
0.00	0	0.000000	0.00
91.76	55	0.000077	30.70
0.2	4	1.2	1.4
.4	.6	1.4	1.6
.6	.8	1.6	1.8
.8	1	1.8	2
1	1	2	3
1.2	1	3	4
1.4	1	4	5
1.6	1	5	10
1.8	1	10	15
2	1	15	20

TOLERANCES: 0
 ANTICIPATED RESIDUES: 100 55 28 13 6 3 1 1 0 0 0 0 0 0 0 0 0 0 0 0
 Acute Exposure = RDV x X = 0.00025 x 1.6 = 0.0004 mg/kg bwt/day
 MOE = NOEL/Exposure = 25 mg/kg bwt/day / 0.0004 mg/kg bwt/day = 62500



13544

033332

Chemical: 1H-1,2,4-Triazole, 1-((2-(2-chloro-4-(4-

PC Code: 128847

HED File Code 11000 Chemistry Reviews

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